REMARKS/ARGUMENTS

Status of the Claims

Claims 1 to 7 and 28 to 35 were previously pending and presented for examination. Claims 1, 7, and 29 are amended herein. Claims 36 to 38 are newly presented. Claims 8 to 27 were previously canceled without prejudice. After entry of these amendments, claims 1 to 7 and 28 to 38 will be pending.

Claims 1 to 7 and 28 to 35 stand rejected under 35 USC §112, first paragraph for an alleged noncompliance with the written description requirement.

Claims 1 to 7 and 28 to 35 stand rejected 35 USC §112, first paragraph for an alleged lack of enablement.

Claims 1, 5, 6, 28, and 29 stand rejected under 35 USC §103(a) as allegedly being unpatentable over U.S. Patent No. 6,180,084 to Rusholahti et al., hereinafter the '084 patent) in view of Sim (Angiogenesis, 1998, hereinafter "Sim").

Support for the Amendments

Claim 1 was amended to set forth that the targeting peptide comprises a sequence from the group consisting of GGGVFWQ (SEQ ID NO:1), HGRVRPH (SEQ ID NO:2), VVLVTSS (SEQ ID NO:3), CLHRGNSC (SEQ ID NO:4), and CRSWNKADNRSC (SEQ ID NO:5). Support for such subject matter is found as previously set forth for claim 3 (p. 27, first full paragraph).

Claim 1 was further amended to set forth that the targeting peptide could comprise functionally equivalent sequences having one or two conservative amino acid substitutions. Support for this subject matter is found *inter alia* in the specification at p. 27, first paragraph, which specifically incorporated by reference a U.S. Patent Application which matured as U.S. Patent No. 6,303,573 and is already of record. Support for this amendment can be found in the '573 patent at col. 7, lines 15-45.

Claim 1 was amended to recite "capable of specifically binding to cardiac vascular endothelium" in place of "that specifically binds to vascular endothelium." Support for this subject matter is found in the previous version of the claim and in the specification at p. 27, first paragraph.

Claims 7 and 29 were amended to recite "chimeric molecule" in place of "protein" to better conform to the antecedent basis in their corresponding intervening claims. Support for this subject matter is found in the previous versions of these claims.

Claims 36 and 37 set forth lengths of the targeting peptide. Support for this subject matter is found *inter alia* in the specification at p. 27, first paragraph. This paragraph specifically incorporated by reference U.S. Patent Application Serial No. 09/326,718 which matured as U.S. Patent No. 6,303,573. Support for this amendment can be found in the '573 patent at col. 6, lines 65-67. This section of the '573 patent sets forth such lengths for the corresponding "homing" peptides.

Accordingly, the Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the Rejection of Claims 1 to 7 and 28 to 35 for Alleged Noncompliance with the Written Description Requirement

In order to expedite prosecution of the instant application and without acquiescing to the position of the Examiner, the Applicants have amended the base claim to set forth a Markush group of the five targeting peptide sequences indicated to be adequately described by the specification and their functionally equivalent modifications having one or two conservative substitutions thereof.

Written support for the functionally equivalent substitution subject matter can be found in the specification at p. 17, first full paragraph. This section of the specification discloses conservative substitutions for the various primary amino acids. The '573 patent, which was specifically incorporated by reference with regard to the targeting peptides, more particularly discloses functionally equivalent modifications having one or two conservative substitutions in the last two paragraphs of col. 7. Methods of making and using such peptides are also disclosed

in the '573 patent. Given the generally much smaller effect of conservative amino acid substitutions on biological activity, and these additional disclosures, one of ordinary skill in the art would recognize that the Applicants were in possession of such targeting peptide subject matter as of the time of filing.

Accordingly, Applicants believe the amended claims comply with the written description requirement and respectfully request reconsideration of the above rejection.

Response to the Rejection of Claims 1 to 7 and 28 to 35 for an Alleged Lack of Enablement.

A. The Grounds for Rejection.

The Action considered the targeting peptide subject matter of the claims to be overly broad in view of the possibly thousands of peptides encompassed and especially as applied to any such peptides which would be structurally unrelated to those set forth in the specification. The Action also posited that the specification exemplified targeting peptides which specifically bound to *cardiac* vascular endothelium, rather than vascular endothelium.

In order to expedite prosecution of the instant application and without acquiescing to the position of the Examiner, the Applicants have amended the base claim. The base claim was amended to set forth a Markush group of the five targeting peptide sequences indicated to be enabled in the Action. The base claim was also been amended to recite *cardiac* vascular endothelium.

The claims were amended to further set forth functionally equivalent modifications of the five targeting amino acid sequences in which the sequences have just one or two *conservative* amino acid substitutions. The enablement of this additional targeting peptide subject matter is discussed below.

B. Standard of Enablement.

As noted by the Examiner, whether undue experimentation is required to practice an invention is typically determined by the "Wands" factors. These factors weigh (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte*

Forman, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

The *Forman/Wands* Analysis

(i) Level of Skill in the Art.

Applicants submit that the level of skill in the art of drug development is high. Such work is typically conducted by research enterprises populated with persons with advanced doctoral and medical training in the relevant fields. More particularly, with regard to the field of targeting peptides, Applicants note that methods of panning for targeting peptides are taught in U.S. Patents Nos. 5,622,699 and *6,180,084,* each to Ruoslahti et al (each already of record). More particularly, Applicants note that cardiac homing or targeting peptides are disclosed in, and much more broadly claimed, in U.S. Patent No. 6,303,573 to Ruoslahti et al. which was incorporated by reference into the Applicant's specification.

(ii) Nature of the Invention.

The invention is in the field of drug development. This field of art, drug development, is traditionally one in which a large volume of compound screening is both typical and routine. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans[1].

(iii) Breadth of the claims.

Applicants have amended the base claim as noted above to address the main thrust of the Examiner's arguments. Thus, the base claim now recites structural limitations for

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[1] *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

the targeting peptides and also recites that the targeting peptides are "capable of specifically binding *cardiac* vascular endothelium."

(iv) Amount of Guidance Presented.

The specification provides adequate guidance for all manipulations required to practice the invention. In particular with respect to the targeting peptides, it discloses the sequences associated with targeting activity, it discloses possible conservative substitutions according to the amino acid, and it sets forth methods of screening peptides in mass for such activity and incorporates by reference (see p. 26, first full paragraph) the '573 patent which also discloses and exemplifies how to screen for such activity.

In this regard, Applicants note that incorporation by reference is no bar to enablement. The MPEP § 2163.07(b) provides:

> [The] Commissioner has considerable discretion to permit the applicant to incorporate information by reference into the specification. The information incorporated by reference at the time of filing is as much a part of the application as filed as if the text were repeated therein.

(v) Working Examples.

The '573 specification provides examples of how to identify targeting peptides in Examples I and II thereof (cols. 21 and 22, respectively).

(vi) State of the Art.

The state of the art is high. The field of chemical drug development has reached a highly advanced state of art due to an understanding of receptor-based mechanisms and the more recent introduction of high throughput screening methods and combinatorial phage methods as illustrated particularly in the '573 patent.

(vii) Unpredictability of the Art.

Chemically-based pharmacological activity are generally governed by structure activity relationships which provide some measure of predictability in the field. Here, the

Applicants have taught the general structures associated with the relevant activity and demonstrated the ability of others to repeatedly find active compounds, as exemplified Examples I and II of the '573 patent.

(viii) Undue Experimentation.

The quantity of experimentation necessary[2] to practice the invention with exemplified and non-exemplified embodiments is what is routinely performed by a person of ordinary skill in the art of drug development.

(ix) Summary and Overall *Forman/Wands* Analysis.

As set forth in the MPEP §2164.01(a), the final step in making the determination that "undue experimentation" would have been needed to make and use the claimed invention is "reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737."

Here, the level of skill for one of ordinary skill in the art is high. The breadth of the claims is substantially reduced as the Applicants have amended the claims to recite targeting peptide subject matter which is substantially narrower than that granted in the '573 patent and only slightly broader than the subject matter which the Examiner acknowledged to be enabled. Furthermore, the invention is in a field of art, drug development, in which one of ordinary skill is highly advanced and in which considerable drug screening is undertaken as a matter of routine. In addition, the field has recently matured and has available to it combinatorial chemistry and high throughput screening methodologies to facilitate such screening on a truly massive scale. Thus, one of ordinary skill in the art would need to do no more than the routine amount of

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[2] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

experimentation in order to identify functionally equivalent targeting peptide sequences having just one or two conservative amino acid substitutions.

Accordingly, the Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 1, 5, 6, 28, and 29 for allegedly unpatentability over the '084 patent in view of Sim.

In order to expedite prosecution of the instant application and without acquiescing to the position of the Examiner, the Applicants have amended the base claim to set forth a Markush group containing the five targeting peptide sequences indicated to be nonobvious over the cited art as well as their functionally equivalent targeting peptide sequences having just one or two conservative amino acid substitutions.

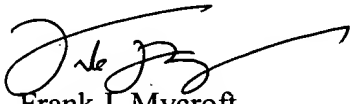
A *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. Applicants do not find the recited peptide sequences of claim 1 in either the '084 patent or the Sim reference. Accordingly, Applicants believe the amendments to the claims satisfy the requirements of 35 U.S.C. §103(a) and respectfully request reconsideration of the above rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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